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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FRANK S. DIGIGLIO, ESQ.
SCULLY, SCOTT, MURPHY AND PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY, NY 11530

EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/624,965	MASTERS ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election of sodium citrate as species of zinc-binding agent in Paper No. 28 is acknowledged.

Claims 28-45 are under examination in the instant office action.

Claim Objections

2. Claim 34 is objected to because of the following informalities: "administration to said patient to an effective amount" should be "administration to said patient an effective amount", perhaps.

Claim 40 is objected to because of the following informalities: "administering said patient to an effective amount" should be "administering to said patient an effective amount", perhaps.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 28-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 28-33 are directed to a method for treating Alzheimer's disease in a patient comprising the step of subjecting said patient to a therapeutically effective amount of an agent which modulates the interaction between a divalent or trivalent cation and/or heparin with amyloid precursor protein (APP). Claims 34-45 are directed to a method for altering or reducing incorrect protease-mediated processing of APP in a patient with Alzheimer's disease by administration of agent which modulates the interaction between a divalent or trivalent cation and/or heparin with APP. The invention is based on a hypothesis that abnormal proteolytic processing of APP is caused by altered interaction between cations, heparin and APP. Such abnormal proteolysis of APP leads to amyloid plaque formation and, consequently, to Alzheimer's disease. Thus, "by manipulating the interaction between cations, preferably zinc, and APP, protease mediated digestion of APP (i.e. APPase activity) is altered" (page 6, second paragraph of the instant specification). It is therefore asserted that administration of an agent, which binds to a divalent or trivalent cation and/or heparin and thus preventing the interaction of these factors with APP and abnormal cleavage of APP, would alter protease-mediated digestion of APP and lead to the treatment of Alzheimer's disease. However, the instant specification fails to provide guidance for such method of treatment or adequate working examples, thus, requiring undue experimentation on part of one skilled in the art to discover how to practice the instant invention as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

The state of the prior art is such that numerous hypotheses exist on etiology of Alzheimer's disease and no known discovered effective treatment. Alzheimer's disease is classically characterized by two brain abnormalities: the presence of neurofibrillary tangles (NFTs) and extracellular deposits of amyloid β (Council et al., 1991, page 441, abstract). At the time of the invention it was disclosed that zinc-deficiency leads to the increase of NFTs and to NFT encephalopathy (Costantindis, 1991, p.31, abstract; Costantindis, 1992, pp.1-14, see specifically p. 5, last sentence). The instant invention is predicated "on the discovery that by manipulating the interaction between cations, preferably zinc, and APP (amyloid precursor protein), protease mediated digestion of APP (i.e. APPase activity) is altered" (page 6, lines 18-20 of the instant specification). At the time of the invention, it is not recognized in the art that any divalent or trivalent cation, or zinc in particular, can prevent "incorrect protease-mediated processing of APP" (claim 40), and obviate amyloid plague formation.

Thus, the state of the art can be characterized as (1) recognizing that zinc deficiency leads to aggravation of one of two major morphological features of Alzheimer's disease, NFTs, and (2) that it was not recognized that zinc obviates formation of amyloid β.

While the skill level in the art is high, the level of predictability is low. There are many factors involved in formation of amyloid β and many ways in which such process is regulated. The working examples of the claimed method of treatment of Alzheimer's disease in the

specification, as originally filed, pertain to the *in vitro* binding assays, profiling of plasma APP, and studies of progression of Alzheimer's disease of patients being treated with increased doses of zinc supplements. Based on the disclosed results, one skilled in the art clearly would not be able to establish therapeutically effective amount of an agent which modulates the interaction between a divalent or trivalent cation and/or heparin with APP. The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that, first, administration of zinc-binding agent would not cause acceleration of NFT formation and lead to progression of Alzheimer's disease, as disclosed in the art, and, second, that because zinc supplementation worsened the symptoms of Alzheimer's disease (page 32-34) zinc deprivation would improve the symptoms.

In addition, Applicant is advised that recitation ""subjecting said patient to a therapeutically effective amount of an agent" broadly encompasses any means of subjection including topical, transdermal or intranasal administration of "an agent". There is no information presented in the instant specification, which would lead a skilled practitioner in treating a patient by "subjecting [a] patient to a therapeutically effective amount" to intranasal sodium citrate administration, for example.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when

there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution. It would require undue experimentation for the skilled artisan to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 28, 34 and 40 are vague and indefinite for recitation "agent modulates the interaction". Term "modulates" is a relative term. Because no point of reference is resented in presented the claims or the instant specification, the metes and bounds of "modulation" cannot be defined.

6. Claim 29 recites the limitation "a zinc-binding agent" in claim 29. There is insufficient antecedent basis for this limitation in the claim.

7. Claims 34 and 40 are further vague and ambiguous for recitation "altering" and "reducing", respectively. These terms are relative terms and until point of reference from which alteration or reduction is expected to be assessed is presented, the metes and bounds of "altering" and "reducing" are undefined.

8. Claims 30-33, 35-39 and 41-45 are indefinite for being dependent from indefinite claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 28-30, 33-37 and 40-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Cardelli et al. (1985) for reasons of record in section 12 of Paper No. 9.

Specifically, claims 28-30, 33-37 and 40-43 are directed to a method for treatment of Alzheimer's disease or a method for altering protease-mediated digestion of APP in a patient with Alzheimer's disease by administration of a zinc-binding agent. According to the instant specification, as originally filed, "[e]xamples of zinc binding agents [...] include [...] EDTA" (page 9, lines 7-10). Publication of Cardelli et al. describes "chelation therapy" for the treatment of Alzheimer's disease, wherein specifically EDTA was administered to two Alzheimer's patients (see page 548-549, Case 1 and Case 2). Applicant's argument that "since EDTA is not capable of crossing the blood brain barrier, the proviso language is redundant and is therefore deleted from the claims" (page 5, first paragraph, of the Response of Paper No. 28) is not

persuasive because for art purposes the interpretation of the claimed subject matter is limited to the administration of a zinc-binding agent, one of which is listed in the instant specification as being EDTA, and Cardelli et all. fully anticipate the claimed method.

10. Claims 28-45 are further rejected under 35 U.S.C. 102(b) as being anticipated by Van Stone et al., 1984.

Claims 28-45 are directed to a method for treatment of Alzheimer's disease or a method for altering protease-mediated digestion of APP in a patient with Alzheimer's disease by oral administration of a sodium citrate. Van Stone et al. disclose oral administration of sodium citrate to patients on chronic hemodialysis (see abstract on page 199 and the whole paper). In applying the prior art, it is noted that the intended use of the claimed method for treatment of Alzheimer's disease without any support by enabling disclosure does not render the prior art methods, which recite the same steps, patentably distinct. Accordingly, claimed invention, taken as a whole, is anticipated by Van Stone et al. because the instant claimed method is limited to oral administration of sodium citrate and this step is entirely described by Van Stone et al..

Claims 28-45 lack novelty over the Van Stone et al. reference because a reference need not have described an actual reduction to practice of an invention in order to serve as an anticipatory reference. See *In re Siveramakrishnan*, 673 F.2d 1383, 1384, 213 USPQ 441, 442 (CCPA 1982); *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985). Moreover, even if a reference does not explicitly set forth every element of the claim, the reference may still be an anticipatory reference if the element is inherent in the disclosure. See *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed Cir 1999). In the instant caes the Van Stone et al. reference explicitly suggests the step of administering sodium citrate to a patient

in a therapeutically effective amount to patients on chronic hemodialysis. Because the instant specification is not enabling for the treatment of Alzheimer's disease and fails to disclose a therapeutically effective amount of sodium citrate to treat Alzheimer's disease, disclosure of Van Stone et al. is anticipatory for disclosing oral administration of sodium citrate.

Art of record

11. Applicant is advised that sodium citrate constitutes one of the most common additives to food and drinks regularly consumed by general population. See Powers et al. (1990), which discloses fluid replacement drinks; Prajapati et al., 1990, butter spread; Cavalier-Salou et al. (1991), cheese. Thus, any Alzheimer's disease patient consuming such food or drinks would inherently be treated by sodium citrate.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D.
May 16, 2003